The role of sulfation in the chemical carcinogenesis by n-hydroxy-arylacetamides

Meerman, Johan Hendrik Nicolaas

SUMMARY

The inhibitors of sulfation, pentachlorophenol (PCP) and 2,6-dichloro-4-nitrophenol (DCNP) are used to study the role of sulfation of the carcinogens N-hydroxy-2-acetylaminofluorene (N-OH-AAF) and N-hydroxy-4-acetylamino-4'-fluorobiphenyl (N-OH-AABP4'F) in the rat in vivo for the covalent binding of these carcinogens to macromolecules in the liver and kidneys, the formation of adducts to DNA and glutathione, and the hepatotoxic action of N-OH-AAF.

PCP and DCNP inhibited the sulfation of N-OH-AAF and N-OH-AABP4'F in vitro by a rat liver cytosolic sulfotransferase already at a concentration of 1 μM; PCP was more inhibitory towards the sulfation of the two carcinogens than was DCNP. Both compounds inhibited the sulfation of N-OH-AAF and N-OH-AABP4'F completely at a concentration of 100 μM (Supplement I and V).

Pretreatment of rats with PCP inhibited the N-O-sulfation of N-OH-AAF and N-OH-AABP4'F in vivo. By consequence, more of a dose of N-OH-AAF or N-OH-AABP4'F is conjugated with glucuronic acid. Pretreatment of rats with PCP also decreased the amount of N-OH-AAF and N-OH-AABP4'F that became covalently bound to macromolecules in the rat liver or kidneys (Supplement I and V): PCP inhibited the formation of the N-acetylated DNA-adducts of N-OH-AAF, 3-(deoxyguanosin-N^2-yl)-2-acetylaminofluorene and N-(deoxyguanosin-8-yl)-2-acetylaminofluorene. The formation of the déacetylated DNA-adduct of N-OH-AAF, N-(deoxyguanosin-8-yl)-2-aminofluorene, which is thought to be formed from another reactive species of N-OH-AAF different from the reactive N-O-sulfate ester, was not affected by PCP (Supplement II).

Besides its hepato-carcinogenic action, N-OH-AAF has also an acute toxic effect on the rat liver. Pretreatment of rats with PCP or DCNP prevented the hepatotoxic effect of N-OH-AAF completely (Supplement III). This indicates that sulfation of N-OH-AAF is responsible for this toxic effect of N-OH-AAF.

Part of a dose of N-OH-AAF is excreted by rats in bile or urine as very hydrophilic metabolites. To investigate whether these unidentified metabolites of N-OH-AAF might be glutathione conjugates, the synthetic analogue of the reactive N-O-sulfate ester of N-OH-AAF, N-acetoxy-2-acetylaminofluorene, was reacted with glutathione in vitro. Four isomeric glutathione conjugates were

formed hereby and their identity was established as 1-, 3-, 4- and 7-(glutathion-S-yl)-2-acetylaminofluorene (Supplement IV). Two of these glutathione conjugates, 1- and 3-(glutathion-S-yl)-2-acetylaminofluorene, were formed in the rat in vivo after administration of N-OH-AAF and are excreted in bile. Their formation could be inhibited by pretreatment of rats with PCP (Supplement IV). This shows that these glutathione conjugates are formed in vivo from the reactive N-O-sulfate conjugate of N-OH-AAF.

A convenient way to administer PCP for a prolonged period of time has been found in the administration of this compound as its sodium salt with the drinking water of rats (Supplement VI). This route of administration may be used for long-term inhibition of N-O-sulfation in a study on the role of N-O-sulfation in the carcinogenesis of N-OH-AAF and other related carcinogens.